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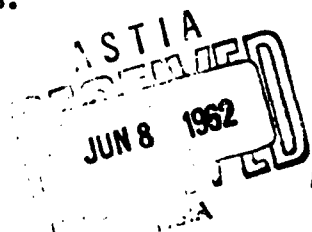
PROGRESS REPORT

- (1) Title of Study: Tissue Transplantation: Homograft antigens, ionizing radiation and other factors influencing homograft survival.
- (2) Period covered by Report: 1 June 1961 - 31 May 1962
- (3) Responsible Investigators: Gustave J. Dammin, M.D.
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1. Introduction

This progress report concerns itself with work of the Brigham Department of Pathology in its laboratories at the Harvard Medical School and with the Departments of Medicine, Surgery and Radiology in the Brigham Hospital. The major research effort of the Department of Pathology relates to transplantation of tissues and organs. In designing a research program which has implications for the military, considerable breadth of activity has been necessary because of the complexity of the field of transplantation. Within the Department of Pathology, the disciplines of immunology, genetics, histochemistry and biochemistry are represented as well as pathologic anatomy. Other disciplines represented in this hospital-wide program, include physiology, pharmacology, surgery, and radiation biology. The list of participants in these studies is a large one. In addition to the principle investigators mentioned, there are other members of the Pathology Department who contribute to these studies. The names of these investigators and those who represent the Departments of Medicine, Surgery and Radiology, are listed in the publications (please see paragraph 11).

The ultimate aim of the program is to achieve successful transplantation of tissues and organs and to so modify the recipient, that indefinite survival may be achieved. The pursuit of these aims has led to a number of observations of basic and practical importance. These are described briefly in the succeeding paragraphs.

2. Transplantation of the Kidney in Man

The best result achieved thus far is in the case of the fraternal twins, JR and AR. It is now over 40 months since AR donated a kidney to JR. This was done following an exposure of JR to two doses of ionizing radiation for a total of 450 r. Evidence of incompatibility was shown by AR's rejection of JR's skin grafts. The early rejection pattern noted in the renal isograft did not occur until approximately 10 months after transplantation. At this time the pattern was well established and presumably reversed by administration of periodic small doses of total body irradiation, and cortisone. No subsequent antibody-depressing measures have been used. The recipient JR, is currently in good health and survives with the renal isograft as his only renal tissue.

Protocols similar to the one just mentioned have been used in subsequent cases here and also by the groups in Paris. Although prolonged survival with function has been obtained in some cases, none has approached the result mentioned above. In our own experience, we have observed in periodic biopsies of the kidney homograft, a variety of patterns which we can interpret as accelerated rejection. These patterns differ from the primary rejection, although there appear to be gradations between the classical primary rejection of a kidney homograft as observed in the dog, and the accelerated rejection pattern as we have seen it in man and as it can be induced by previous sensitization of the canine recipient.

Total body irradiation is known to suppress the primary immune response but has little effect on the secondary response. This has been shown in man and the experimental animals. On the other hand, 6-mercaptopurine and related anti-metabolites have been shown to alter the secondary or anamnestic response. Since most of our potential recipients have received blood transfusions, and therefore have been sensitized because of the presence of antigens in leukocytes, it is plain that we can expect a rejection pattern which is different from the primary one. The expectation that 6-mercaptopurine might provide a better recipient under these circumstances, has been borne out by recent studies. We have observed the early phases of rejection reversed by administration of 6-mercaptopurine. In our current case, the patient is now in the eighth post-transplant week having been given 6-mercaptopurine, followed by

Imuran (BW57-322) and occasional actinomycin C. This represents the longest survival obtained in man with chemical modification of the recipient.

It is likely that we are approaching a state of tolerance rather than one of adaptation. It appears from studies in the dog, that a delicate balance has been achieved, and that this balance may be disturbed by the addition of antigen in the form of a skin graft. The course of a skin graft from the kidney donor will provide valuable information. It has been shown to alter the course of a kidney homograft at the same time that it shows a pattern of delayed rejection. If adaptation were to occur, then the course would be one of a primary rejection. If sensitization has been induced, then rejection of a skin graft would be accelerated. If tolerance of a high degree has been induced, then there should be markedly prolonged survival of the skin graft from the kidney donor when placed upon the modified recipient.

3. Transplantation of the Kidney in the Dog

These studies have been conducted with Dr. Joseph E. Murray and his staff. Dr. G. Alexandre and Dr. K. Nilsson are currently active in this program. The major experience during this year has been with a combination of 6-mercaptopurine given initially and followed by oral doses of Imuran and periodic administration of actinomycin C. The mean survival time of function of the renal homograft has been 58 days with 3 dogs showing survival of the graft for over 3 months. In these subjects, the homograft is the only renal tissue, the recipient's own kidneys having been removed at the time of transplantation. Of special interest in these long survivors, is the effect of a skin graft from the donor on the function of the graft as mentioned above. Although biopsies of the kidney graft have not been done at this time, function becomes impaired. This can be reversed by the administration of actinomycin C. In the few subjects so studied, there has been prolonged survival of the skin graft indicating possibly the combination of some level of tolerance and the effect of the continued administration of Imuran.

In more recent experiments, Imuran has been combined with azaserine. Imuran blocks incorporation of preformed purines into nucleic acids and azaserine acts earlier in purine synthesis. In the first 8 dogs studied with this plan of chemical modification, 4 of 8 dogs have had survival of the kidney homograft for over 60 days. There is indication that cortisone may enhance the effect of actinomycin C in reversing rejection and this will be pursued further. Since actinomycin D is more potent than actinomycin C, later experiments may involve the use of this cytotoxic agent.

Other studies have been directed toward identifying the features of rejection when the canine recipient has been sensitized by antigens from the donor. In one group of experiments conducted with Dr. Brownell Wheeler, cross circulation was used as a means of sensitization. Nine days after a 1-hour cross-circulation, crossed kidney homografts were performed. None functioned for more than 1 day and these showed patterns which included interstitial edema, focal infiltration with mononuclear cells and degeneration of tubular epithelium. In an experiment conducted with Dr. Nilsson, a potential recipient of a kidney graft received spleen cells from 6 donor dogs. Following this a kidney homograft was carried out and this showed a pattern of accelerated rejection. This was taken as evidence for a sharing of transplantation antigens among dogs. In studies with Dr. B. Altman, it was clear that sensitization of the recipient through skin or a previous kidney homograft resulted in accelerated rejection which had its basis in humoral components of the blood and that this sensitization bore no relationship to the dog's blood group antigens.

Attempts will be made to modify rejection as it occurs under these circumstances.

4. Transplantation of the Skin in Man.

Our laboratory has assisted in extensive studies of the transplantation of the skin in man. First, the features of the course of the autograft in man were detailed. It was plain from this, that certain alterations unless understood, might be regarded as evidence of rejection as seen in homografts. The homograft in man also was studied, and here it was shown that varying numbers of transplantation antigens are shared among individuals. The features of each type of rejection follow a fairly standard pattern and by histologic means it is possible to identify exactly, primary rejection, accelerated rejection and also "white graft" rejection. These observations are important in determining how closely individuals may be related one to another. For example, if two individuals are considered as potential donor and recipient of a kidney homograft, if the skin of one is placed on an indifferent recipient, and a skin graft from the other is placed on the indifferent recipient two weeks after the first graft, then, if "white graft" rejection occurs, this identifies the two individuals as having a close genetic relationship one to another. If the second graft follows a course of primary rejection, then the two individuals are genetically disparate.

5. Transplantation of the Liver in the Dog

In these studies, 35 dogs were used as subjects for homotransplantation, 27 for autotransplantation and 13 as sham transplants. The third group was added because there was initially poor survival after autotransplantation. Some of the difficulties with the surgical procedures have been described in previous reports. As technique improved, so did survival and it became possible to identify features of rejection of the liver homotransplant. The hepatectomized dog seldom survives more than 24 hours. The liver homotransplant proves temporarily life-sustaining as a functional organ. Failure of the transplant relates to the infiltration of cells from the recipient with a pattern resembling that seen in the kidney homograft. Anatomic findings in homografts and autografts are similar for the first 3 days after transplantation. Following this, mononuclear cells appear in the liver homograft. It was not possible to identify any lesions representative of a graft-versus-host reaction. These were sought because of the immunologic potential of the liver. Further studies of the liver homograft in the dog may be undertaken after chemical modification of the canine recipient of a renal homograft has been improved further.

6. Transplantation of the Spleen in the Dog.

These studies were undertaken with a view to establishing a splenic homograft which, if it were tolerated, would make this recipient a host for other organs from the same donor. Although it is possible to establish a state of mutual tolerance between donor and recipient when dealing with pure mouse lines, whether this was possible in a large mammal had to be determined. In the unmodified recipient of a splenic homograft, there appeared to be two phases, the first representing a graft-versus-host reaction of possibly 2 days duration, this being followed by rejection of the canine splenic homograft and characterized by the entrance of cells from the recipient. Rejection usually progressed rapidly so that by day 7 - 9, the homograft was completely necrotic. It was not possible to identify a specific vascular component in the rejection process. When the recipient was modified by nitrogen mustard, there was prolonged survival of the spleen architecturally. However, few of the recipients survived long enough to determine the nature of the terminal process. A protocol for administration of nitrogen mustard which led to prolonged suppression of the lymph nodes and marrow had been devised. Despite this, few of the recipients survived into the second week and only one survived into the fourth post-transplant week. However, it was possible to identify follicular architecture for much longer periods in the homograft when the recipient had received

nitrogen mustard. The possibility exists that there was a continuation of a graft-versus-host reaction when the recipient was given nitrogen mustard because it appeared that there was prolonged suppression of both marrow and lymph nodes in these subjects receiving nitrogen mustard and also a splenic homograft. Here again, it may be possible to prolong survival of both graft and recipient through modification with antimetabolites, rather than with primary cytotoxic agents. When more experience has been gained with Imuran and azaserine, further experiments with the canine splenic homograft may be undertaken.

7. Fractions of Tissues and Cells Active Antigenically in a Homologous System

Newer methods of fractionation of mouse spleen cells have been used. Antigenicity of these fractions in a homologous system has been compared with that of whole spleen cells. With separation of constituents from sucrose suspensions at various speeds, it has been found that antigenic activity is found in components which must be almost entirely cytoplasmic in origin. Chemical analyses of active fractions still show that major components are protein and lipid, with a minor fraction consisting of carbohydrate. Cells of other organs will be tested for antigenicity after fractionation to determine relative antigenicity among organs. It has been determined already, that lymph node cells are the most antigenic when whole cells are used in the assay. Less antigenic are spleen cells, thymus cells and bone marrow cells. Preparations of high stability and antigenicity will be tested for their ability to induce tolerance in the neonatal mouse and in the modified adult mouse.

8. Immunologic Capacities of Tissues

Use of the mouse kidney bed has continued in evaluation of graft-versus-host reactions. In these experiments, parent tissue is the donor and the F-1 hybrid is the recipient. Under these circumstances, there can be only a graft-versus-host reaction, because the recipient possesses all of the antigens represented in the parent tissues. As already reported, we have no evidence that the kidney as a homograft can react against the host. On the other hand, when splenic tissue is the homograft, there is reactivity in the follicles suggesting that even as a tissue, spleen is capable of reacting against the host. When the parent as donor is sensitized by F-1 cells, then the graft-versus-host reaction is even more marked.

9. Synthetic Polypeptides as Antigens

This work has been carried out by Dr. Gill in the laboratories of Dr. Paul Doty at Harvard University. Some phases of the work have been done in our contract-supported laboratory. The synthetic polypeptides serve well as model systems for an understanding of the chemical basis of antigenicity, and identification of such determinants will have a bearing on problems of transplantation. Of particular interest is the antibody formed to synthetic polypeptides. Antibodies to a variety of synthetic polypeptides can be studied for their cytotoxicity against mammalian cells. We have already observed that certain of the polypeptides have antigenic resemblances to substances which the rabbit encounters in nature. This was noted with a polypeptide with the following amino acid composition, G56L38T6.

It is important to determine which high molecular weight polypeptides lack antigenicity and therefore may serve as blood protein substitutes. Polypeptides with such properties may be identified through isotope labeling and determination of their pattern of elimination by the experimental animal.

10. Summary

In the paragraphs above are outlined the various approaches which have been used to seek a modification of the host in order that there may be prolonged

functional survival of tissues and organs as homografts. The most encouraging approaches thus far constitute modification of the host with an analog of 6-mercaptapurine and the use of azaserine. The most recent results in man have offered hope of possibly achieving a state of mutual tolerance between the kidney homograft and the host. Chemical modification of the host appears to offer more promise than suppression of the immune response through agents such as ionizing radiation and nitrogen mustard. Basic information on immune response has been gained from these studies. The investigation of synthetic polypeptides of known amino acid composition may provide information on antigenic determinants in mammalian cells and also offer information on the characteristics of antibodies as they are elicited in response to antigens of known constitution.

11. List of Publications

- Couch, H.P., McBride, R.A., Dammin, G.J., and Murray, J.E.: Observations on the nature of the enlargement, the regeneration of the nerves, and the function of the canine renal autograft. *Brit. J. Exper. Path.* 42: 106, 1961.
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- Friedman, E.A., Retan, J.W., Marshall, D.C., Henry, L., and Merrill, J.P.: Accelerated skin graft rejection in humans preimmunized with leukocytes. *Fed. Proc.* 20: 33, 1961.
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- Wheeler, H.B., Balankura, O., Pendover, J.E., Greenberg, J.B., Dammin, G.J., and Moore, F.D.: The homograft response to whole organ transplantation of the canine spleen. *J. Surgical Res.* 2: 114, 1962.

ABSTRACT

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1. Preparing Institution:	Harvard Medical School, Boston 15, Mass.
2. Title of Report:	Tissue Transplantation: Homograft antigens, ionizing radiation and other factors influencing homograft survival.
3. Principal Investigators:	G. J. Darman, J. M. Corson, and L. T. Mann
4. Number of pages, and date:	5 pages, 1 June 1962
5. Contract Number:	DA-49-193-MD-2061
6. Supported by:	United States Army Medical Research and Development Command Department of the Army, Washington 25, D.C.

Summarized in this abstract is work done independently by the principal investigators, and also that conducted with representatives of other departments in the tissue/organ transplantation program (surgery - Drs. F. D. Moore, J. E. Murray, and R. Wilson; medicine - Drs. J. P. Merrill and E. Hager; radiology - Dr. J. B. Dealy).

Modifications have been made in the method for extracting antigens from mouse spleen cells. The essential constituents of this active fraction are protein and lipid, as previously reported. The newer procedure for preparation of the antigenic fraction is simpler and provides a fraction which retains antigenicity longer on storage.

In further study of the canine splenic homograft, it was concluded that an early graft versus host reaction was present for a period probably not exceeding 48 hours. This was followed promptly by a progressive increase in cellularity of the splenic homograft. Suppression of the host's marrow and lymphoid tissues with nitrogen mustard prevented the lymphocytic and plasmocytic infiltration of the splenic homograft and prolonged its survival. Few dogs survived long enough to determine precisely how the host was modified, but it did appear that there might be a prolongation of the graft versus host response induced by the nitrogen mustard. It was plain that the aim of attaining a state of mutual tolerance had not been achieved, and for this reason no further experiments of this design have been carried out.

The best survival achieved thus far for the canine renal homograft has followed a program consisting of the initial administration of 6 mercaptopurine, with BW57-322 given as a daily dose, with periodic addition of Actinomycin C. With this program, more than half of the dogs survived more than 30 days, with the renal homograft as the only renal tissue in the recipient. A similar program has been followed in man for the first time and has resulted in the longest survival obtained thus far with chemical treatment only.

The characteristics of synthetic polypeptides as antigens have been defined further. Amino acid content as well as sequence are important determinants of antigenicity. This is borne out also by examination of the inhibitory effects on antigen-antibody combination by amino acids and dipeptides.

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In further study of the canine splenic homograft, it was concluded that an early graft versus host reaction was present for a period probably not exceeding 48 hours. This was followed promptly by a progressive increase in cellularity of the splenic homograft. Suppression of the host's marrow and lymphoid tissues with nitrogen mustard prevented the lymphocytic and plasmocytic infiltration of the splenic homograft and prolonged its survival. Few dogs survived long enough to determine precisely how the host was modified, but it did appear that there might be a prolongation of the graft versus host response induced by the nitrogen mustard. It was plain that the aim of attaining a state of mutual tolerance had not been achieved, and for this reason no further experiments of this design have been carried out.

The best survival achieved thus far for the canine renal homograft has followed a program consisting of the initial administration of 6 mercaptopurine, with BW57-322 given as a daily dose, with periodic addition of Actinomycin C. With this program, more than half of the dogs survived more than 30 days, with the renal homograft as the only renal tissue in the recipient. A similar program has been followed in man for the first time and has resulted in the longest survival obtained thus far with chemical treatment only.

The characteristics of synthetic polypeptides as antigens have been defined further. Amino acid content as well as sequence are important determinants of antigenicity. This is borne out also by examination of the inhibitory effects on antigen-antibody combination by amino acids and dipeptides.

ABSTRACT

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1. Preparing Institution:	Harvard Medical School, Boston 15, Mass.
2. Title of Report:	Tissue Transplantation: Homograft antigens, ionizing radiation and other factors influencing homograft survival.
3. Principal Investigators:	G. J. Dammin, J. M. Corson, and L. T. Mann
4. Number of pages, and date:	5 pages, 1 June 1962
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